

Infectious Complications of Open Type III Tibial Fractures among Combat Casualties

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Background. Combat is associated with high-energy explosive injuries, often resulting in open tibial fractures complicated by nonunion and infection. We characterize the infections seen in conjunction with combat-associated type III tibial fractures.

Methods. We performed a retrospective medical records review to identify US military service members wounded in Iraq or Afghanistan with open diaphyseal tibial fractures who were admitted to our facility (Brooke Army Medical Center, Fort Sam Houston, Texas) between March 2003 and September 2006.

Results. Of the 62 patients with open tibial fractures who were identified in our initial search, 40 had fractures that met our inclusion criteria as type III diaphyseal tibial fractures. Three patients were excluded because their fractures were managed with early limb amputation, and 2 were excluded because of incomplete follow-up records. Twenty-seven of these 35 patients had at least 1 organism present in initial deep-wound cultures that were performed at admission to the hospital. The pathogens that were identified most frequently were *Acinetobacter*, *Enterobacter* species, and *Pseudomonas aeruginosa*. Thirteen of the 35 patients had union times of >9 months that appeared to be associated with infection. None of the gram-negative bacteria identified in the initial wound cultures were recovered again at the time of a second operation; however, all patients had at least 1 staphylococcal organism. One patient had an organism present during initial culture and in the nonunion wound; this organism was a methicillin-resistant *Staphylococcus aureus* strain that was inadvertently not treated. Five of 35 patients ultimately required limb amputation, with infectious complications cited as the reason for amputation in 4 of these cases.

Conclusions. Combat-associated type III tibial fractures are predominantly associated with infections due to gram-negative organisms, and these infections are generally successfully treated. Recurrent infections are predominantly due to staphylococci.

Since the beginning of American military operations in Afghanistan and Iraq, there have been >21,000 injuries among US service members [1]. The presence of surgical care near the point of injury, the rapid evacuation of the wounded to medical care, and the use of body armor has culminated in greater numbers of casualties surviving their initial injury. Orthopedic injuries have made up ~65% of the total number of injuries during every major conflict in which the US military has par-

ticipated from World War I to its operations in Somalia. This remains true in the current conflicts in Iraq (Operation Iraqi Freedom [OIF]) and Afghanistan (Operation Enduring Freedom [OEF]), both during the early stages of the conflicts and during stability operations [2–4].

The soft-tissue defects produced in conjunction with open fractures in war-related trauma, contamination of wounds at the time of injury, and the associated prolonged hospital courses with potential exposure to nosocomial pathogens all contribute to the frequency of infectious complications among combat casualties. Early and aggressive management of these extremity wounds, starting with interventions near the battlefield, have resulted in reduced mortality and fewer amputations, but wound and bone infections remain an important source of morbidity [5]. The etiology of war wound infections has changed from the clostridial infections seen before World War I to the polymicrobial

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infections seen during the Vietnam conflict, with an increase in the frequency of drug-resistant infection. Recovery of multidrug-resistant gram-negative organisms, notably *Acinetobacter calcoaceticus-baumannii* complex, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, is increasingly being reported from the wounds of OIF and OEF casualties [6].

Infectious complications of open fractures can complicate bone healing. Delayed union and nonunion of the diaphyses of long bones is a serious complication of traumatic extremity wounds, with local infection as one of the potential factors inhibiting fracture union. This may be observed following open fractures of the tibia [7].

Gustilo and Anderson [8] classified open fractures into 3 types. Type I fractures are defined as those with a laceration of ≤ 1 cm with minimal soft-tissue damage and no gross contamination. Type II fractures have lacerations of >1 cm with moderate soft-tissue damage. Type III fractures are high-energy injuries, typically with bone comminution or loss and lacerations of >10 cm. There are 3 type III subtypes: IIIA, which involves extensive soft-tissue injury but adequate soft-tissue coverage; IIIB, which involves extensive soft-tissue injury along with bone exposure requiring soft-tissue coverage; and IIIC, which involves extensive soft-tissue damage and the need for arterial repair. With aggressive surgical intervention and treatment of local infections, most cases of delayed union eventually result in a functional limb. Type III tibial fractures have a reported infection rate of 6%–39%, whereas the associated amputation rate has historically been $<10\%$ [9–12].

The high-energy weaponry of combat can result in massive tissue damage. In addition, increasingly drug-resistant bacteria are being recovered from OIF and OEF casualties. At this time, it is unclear what role infections are playing in the outcome of these catastrophic injuries. We set out to characterize the bacteria recovered from these wounds near the time of injury and to determine if these bacteria contributed to deep infections, prolonged healing times, and/or amputation.

METHODS

All US military service members admitted to our facility ((Brooke Army Medical Center, Fort Sam Houston, Texas) between March 2003 and August 2006 who were wounded in OIF or OEF with type III open diaphyseal tibial fractures were identified through electronic medical records. Data for these patients were retrospectively extracted from inpatient and outpatient medical records for date of injury, fracture site, antibiotic prophylaxis on arrival at our institution, initial surgical management, specimen type (bone or tissue), initial culture results and drug-susceptibility results, surgical and pharmacological treatment of early wound infections, response to therapy, follow-up culture results, imaging results, and definitive management. Records were reviewed from admission to Brooke

Army Medical Center through the patient's last known follow-up visit at any hospital or clinic site within the military health care system.

All patients received irrigation and debridement procedures before arrival at our facility. Samples for initial cultures were obtained in the operating room from deep tissues during each patient's first surgical debridement on arrival at our facility. A patient was defined as having an initial infection if an organism was isolated from these first wound samples, if there were findings from the surgical report (such as purulent or necrotic tissue or a sinus tract) consistent with infection, and a course of antimicrobial agents was prescribed. In each case, these decisions to treat were made in conjunction with an infectious disease specialist. After initial antibiotic therapy was completed, any pathogens identified in surgical cultures obtained because of the need for an additional operative procedure (e.g., purulent drainage from surgical wound, need for bone grafting to repair bony defect, or additional fixation to obtain union) are described here as reassessment cultures. We were not able to obtain detailed surgical reports or results of cultures that may have been obtained before arrival at our facility for these patients because of a number of limitations associated with care provided in a combat region. These include the great volume of critically injured patients and frequent turnover of staff, which limits provider-to-provider communication about patients; the fact that data are not recorded in an electronic medical record accessible to the study investigators in the United States; and the fact that any paper records remain at these overseas facilities. As a result, we did not include culture data obtained before arrival at our facility in the final analysis for any patient.

RESULTS

There were 62 tibial fractures associated with OIF and OEF casualties admitted to our facility during the study period. Forty patients had type III open fractures, but 3 patients were excluded because their initial fracture management included amputation, and 2 patients were excluded because of incomplete medical records. Thirty-five patients with traumatic open type III diaphyseal tibial fractures obtained during OIF and OEF were included in the final analysis (figure 1). The group was predominantly male (33 of 35 patients), with a tendency to have more-severe injuries (24 fractures were classified as type IIIB, compared with only 11 type IIIA fractures). The mechanism of injury was an explosive device in 27 cases (77%). The remaining 8 cases of open fracture occurred as the result of other trauma, including motor vehicle collisions and gunshot wounds. In each case, initial management of the open tibial fracture included wound debridement and placement of an external fixation device in a military hospital in the combat zone before transfer to the US military tertiary care referral

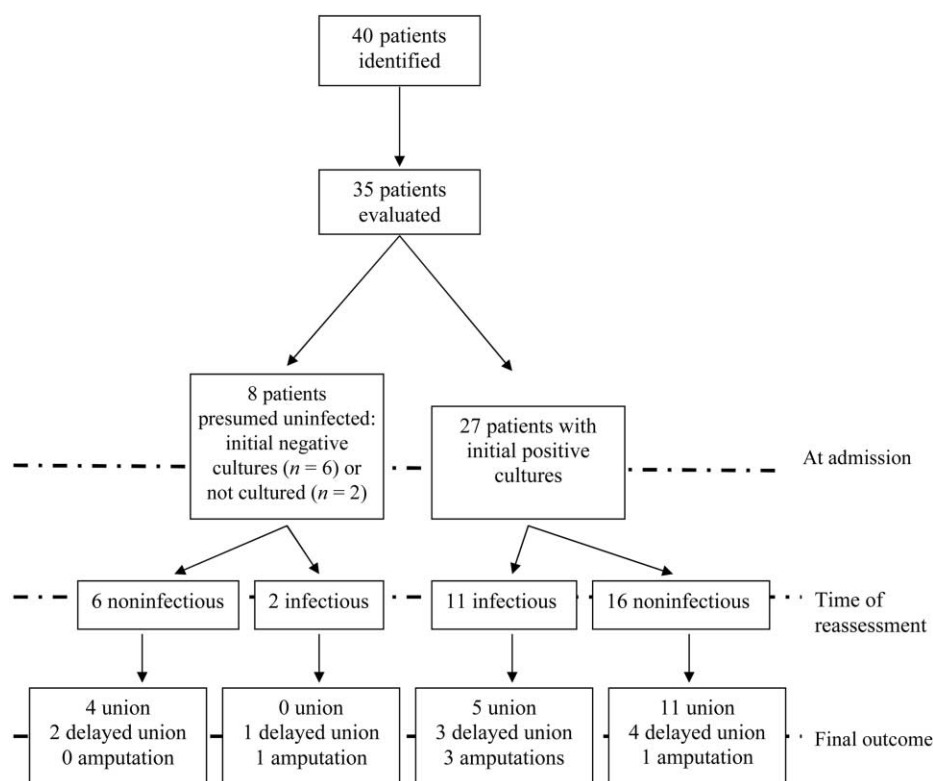


Figure 1. Outcomes of wounded US military personnel with type III open tibial fractures

center in Germany. Initial management in the combat zone and in Germany also included perioperative coverage of gram-positive organisms with cefazolin or vancomycin for all patients, administered at the time of each irrigation and debridement. Typically, after a brief stay in Germany, including a single additional irrigation and debridement procedure, patients were moved to a military medical treatment center in the United States, where they received the majority of their care, including definitive fracture therapy, treatment of any comorbid injuries or illness, and management of any complications. The mean evacuation time from injury to arrival in the United States was 7.4 days, which is consistent with a previously reported OEF casualty series in which the mean evacuation time was 7.9 days; the mean number of combined procedures in the combat zone and in Germany was 2.6 [13]. Follow-up ranged from 4 to 43 months, with a mean of 19.5 months and a median of 18 months.

Twenty-seven (77%) of 35 patients had at least 1 organism present in initial deep-wound cultures (figure 1). Of the 8 patients classified as uninfected at initial presentation, 2 underwent surgical management, including surgical debridement and external fixation, but did not have culture samples obtained on presentation at Brooke Army Medical Center or receive any antimicrobial therapy. One patient had a persistent nonunion, whereas the other patient recovered with appropriate union of

the tibia. The most common organisms in these initial cultures were *A. calcoaceticus-baumannii* complex, *Enterobacter* species, and *P. aeruginosa* (table 1). Gram-positive bacteria were less frequently recovered. Ten cases (37%) were polymicrobial infections. All 27 patients with positive culture results received extended courses of antimicrobial agents. All but 1 patient received antimicrobials active against the bacteria identified. Overall, 24 (89%) of 27 patients received therapy for osteomyelitis. The remaining 3 patients were treated for deep-wound infection. The median number of days of antibiotic therapy for all 27 patients was 42 days.

Of the 35 patients included in the study, 13 had cases that were complicated by deep-wound infections at reassessment; of these, 11 had had previous infections and 2 had not (figure 1; table 2). No gram-negative pathogen identified during initial presentation was recovered in a subsequent infection (tables 1 and 2). Only 1 patient had an organism recovered from subsequent cultures that was also recovered by initial culturing. This patient (patient 12) was a 22-year-old man whose early deep-wound cultures yielded methicillin-resistant *Staphylococcus aureus* (MRSA) that was inadvertently not treated (table 2). In the remaining 12 patients who developed infectious complications, these complications were predominantly due to staphylococcal infection. All cases were associated with the presence of external-fixator pin tracks or an indwelling intrame-

Table 1. Microbiological content of cultures obtained from Operation Iraqi Freedom and Operation Enduring Freedom casualties at Brooke Army Medical Center who had type III open tibial fractures that were complicated by infection.

Organism	No. of patients, by time point	
	Presentation	Reassessment ^a
Gram-negative		
<i>Acinetobacter calcoaceticus-baumannii</i> complex	13	0
<i>Enterobacter</i> species	6	0
<i>Pseudomonas aeruginosa</i>	5	3
<i>Klebsiella pneumoniae</i>	3	0
<i>Escherichia coli</i>	2	1
<i>Stenotrophomonas maltophilia</i>	1	0
Unknown	1	0
Gram-positive		
Coagulase-negative staphylococci	3	7
<i>Enterococcus</i> species	3	0
MSSA	2 ^b	5
MRSA	1	4 ^a
Other	2 ^c	4 ^d

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*.

^a Only 1 patient had the same bacteria (MRSA) noted in initial cultures and reassessment cultures.

^b Initial cultures included recovery of organisms for which antimicrobial susceptibilities were not determined.

^c Includes *Bacillus* species and viridans streptococci.

^d Includes *Peptostreptococcus magnus*, *Corynebacterium* species, group G streptococci, and *Propionibacterium acnes*.

dullary nail, and all patients except 1 of the 35 who were evaluated had external-fixator pins or an intramedullary nail present during their hospitalization. Only 3 of these patients had received any prolonged antimicrobial therapy (other than prophylactic cefazolin administered perioperatively) for another organism that was also active against the staphylococcal species that was subsequently recovered at nonunion. These included 1 patient who was treated with vancomycin for initial coagulase-negative staphylococcal wound infection who subsequently developed MRSA infection; 1 patient who was treated with ampicillin-sulbactam for *A. calcoaceticus-baumannii* complex, which had activity against the methicillin-susceptible *S. aureus* (MSSA) infection that he later developed; and a third patient who was treated with imipenem for 12 days for *K. pneumoniae* infection who later developed MSSA infection.

In all, 5 of 35 patients had such severe remaining bone and/or soft-tissue defects that they ultimately required amputation of the limb. Infection was a contributing factor to amputation in 4 of these 5 cases. In 3 of these cases (patients 2, 4, and 9), amputation followed recurrent infection (table 2). The fourth patient (patient 7), whose initial cultures yielded negative results, underwent limb amputation following infection with MSSA and *P. aeruginosa* and continued to have recurrent MRSA and MSSA infections of his stump even after amputation (table

2). In the outlying case of limb amputation, lack of union in the tibia was not associated with evidence of infection.

DISCUSSION

Casualties associated with the current conflicts in Iraq and Afghanistan are frequently characterized by orthopedic injuries, often complicated by bacterial infections resistant to multiple antimicrobial drugs. In our characterization of the bacteria infecting open tibial injuries sustained on the battlefield, gram-negative bacteria were the predominant organism identified on initial culture. Although surgical management and directed antimicrobial therapy cleared the bacteria initially identified, 35% of patients had subsequent evidence of infection. All patients with subsequent evidence of infection had gram-positive bacteria recovered, with 3 patients also having evidence of new *P. aeruginosa* infections. There was no recurrence of the *A. calcoaceticus-baumannii* complex or *Klebsiella*, *Enterobacter*, or *Pseudomonas* species treated initially. Only 1 patient had a recurrence of the initially identified bacterium. In that case, caused by MRSA infection, the patient did not receive antimicrobial therapy directed at the pathogen initially recovered. Of the 13 patients with recurrent infections, 4 (31%) underwent amputation. Our study underscores the substantial morbidity

Table 2. Characterization of courses for patients with type III tibial fractures complicated by infection and delayed union.

Patient	Age (sex, type of fracture)	Initial pathogen(s) (period from injury to collection of culture sample, days)	Antimicrobial therapy (duration of therapy, weeks)	Delayed union pathogen(s) (period from injury to collection of culture sample, months)	Outcome (time after injury, months) ^a
1	45 (M, IIIa)	None (9)	None	MSSA, <i>Propionibacterium acnes</i> (9)	Delayed union (15)
2	33 (M, IIIa)	Acb (6)	Ampicillin-sulbactam (6)	CoNS (2, 4); <i>Peptostreptococcus magnus</i> (4); MSSA (10, 15); <i>Escherichia coli</i> (10) ^b	Amputation (18)
3	24 (M, IIIb)	<i>Pseudomonas aeruginosa</i> (CoNS and viridans streptococci recovered from broth) (12)	Gentamicin, piperacillin-tazobactam (6)	<i>Corynebacterium</i> species (recovered from broth) (2); CoNS (recovered from broth) (3)	Union (31)
4	34 (M, IIIb)	Acb (5)	Imipenem-cilastatin (7)	<i>P. aeruginosa</i> (3); CoNS (4)	Amputation (10)
5	40 (M, IIIb)	Acb (8)	Imipenem-cilastatin (6)	CoNS (3)	Delayed union (5)
6	22 (M, IIIa)	Acb, <i>Enterobacter</i> species (6)	Imipenem-cilastatin (8)	CoNS (5), group G streptococci (13)	Union (19)
7	22 (M, IIIa)	None	NA	MSSA (4); <i>P. aeruginosa</i> (6)	Amputation (9) ^c
8	25 (M, IIIb)	CoNS (<i>Escherichia coli</i> and <i>Enterobacter</i> species recovered from broth) (30)	Imipenem-cilastatin (2), amikacin (1), vancomycin (0.5)	MRSA (3)	Union (15)
9	22 (M, IIIb)	Acb, <i>Enterococcus</i> species (3)	Amikacin, ampicillin-sulbactam (6)	MSSA (13)	Amputation (13)
10	20 (M, IIIb)	ESBL <i>Klebsiella pneumoniae</i> (3)	Ampicillin, gentamicin, imipenem-cilastatin (2) ^d	MSSA (16)	Union (25)
11	27 (M, IIIb)	Acb (15)	Imipenem-cilastatin (8)	MRSA (6), CoNS (12)	Delayed union (21)
12	22 (M, IIIa)	MRSA (28)	None	MRSA (3)	Delayed union (12)
13	23 (M, IIIb)	Acb, <i>Enterobacter cloacae</i> (10)	Amikacin, meropenem (2.5)	<i>P. aeruginosa</i> (1), MRSA (2), CoNS (3)	Union (40)

NOTE. Acb, *Acinetobacter calcoaceticus-baumannii* complex; CoNS, coagulase-negative staphylococci; ESBL, extended-spectrum β -lactamase-producing; M, male; MRSA, methicillin resistant *Staphylococcus aureus*; MSSA, methicillin susceptible *S. aureus*; NA, not applicable.

^a At last follow-up visit.

^b No therapy for *E. coli* infection was provided; no evidence of *E. coli* on follow-up cultures, including cultures at time of amputation.

^c Recurrent MRSA and MSSA infections of remaining stump.

^d Ampicillin was administered simultaneously for treatment of an enterococcal deep-wound infection at another site.

that infection can contribute to the process of fracture union, especially in the setting of traumatic injury occurring during combat operations.

Overall, there was a higher prevalence of wound infection (77%) in this series of patients than that reported for other combat-associated open fracture injuries or for civilian type III tibial injuries [10–14]. Despite this high rate of early infection, patients generally cleared the initial infection. Of the 27 patients with initial wound infection, nearly one-half developed a subsequent infection, but of these patients, only 1 developed subsequent infection due to an organism isolated from the original cultures. Subsequent infections were much more likely than the original infections to be due to gram-positive organisms. Earlier tibial nonunion studies have also reported *S. aureus* and *P. aeruginosa* to be the pathogens most associated with infection [15].

Since the onset of OIF and OEF, a number of reports have described drug-resistant pathogens, notably *A. calcoaceticus-baumannii* complex, infecting combat casualties [7, 16, 17]. Previous studies have shown that gram-positive organisms predominate in the cultures of traumatic wounds at the time of injury. In a case series of 61 wounds cultured at the time of injury in Iraq during OIF, 39 of these wounds showed contamination, and 37 (93%) of these cases of wound contamination were due to gram-positive organisms [2]. This is supported by data from the Vietnam conflict that reported that gram-positive bacteria were recovered from wounds near the time of injury [18]. When casualties underwent culture of their wounds after 5 days of surgical care and antimicrobial therapy, the spectrum of pathogens transitioned to predominantly gram-negative bacteria. The presence of gram-negative bacteria in nearly 73% of our cases mirrors the pathogens recovered from wounds 5 days after injury in the Vietnam conflict, which is the same time span during which culture samples were obtained from many of our casualties. This shift is possibly related to the fact that all 35 patients in this case series received prophylactic cefazolin at the time of their initial wound management, which likely reduced the burden of disease attributed to low-pathogenicity gram-positive organisms early in their treatment course and increased the role of nosocomial pathogens. However, it remains unclear whether these wounds become contaminated at the time of injury, during initial management, or during transfer of care through each echelon of care before reaching a medical treatment facility in the United States [19, 20].

This study also supports previous studies citing the low pathogenicity of *A. calcoaceticus-baumannii* complex in wound infections [16, 17]. *A. calcoaceticus-baumannii* complex was isolated 13 times from initial wound cultures obtained at our facility (32.5% of cases). However, after initial treatment, *A. calcoaceticus-baumannii* complex was never isolated from any

reassessment wound cultures and did not appear to directly contribute to any substantial morbidity (namely, persistent nonunion or amputation). In addition, *A. calcoaceticus-baumannii* complex did not require dual therapy to resolve the infection, supporting previously reports [16].

One of the major limitations of this study was our inability to obtain the details of each patient's management course before transfer to our facility. These details, particularly the results of cultures obtained at the time of injury and during each subsequent debridement performed before transfer to a medical treatment facility, would have provided important clues regarding changes in the bacteriological content of early wounds, as well as insight into exactly when and how wound contamination occurs in these wounded soldiers. The small number of patients included in this study also precludes the development of any generalizations based on our findings but, nonetheless, provides some interesting avenues for pursuit in future studies.

Several questions require further consideration, in particular the striking finding that all of the patients with subsequent infections in our case series had *Staphylococcus* species recovered from culture. Current management of mangled extremity trauma, especially type III fractures, includes short-course antimicrobial therapy with coverage of both gram-negative and gram-positive organisms [21]. It remains unanswered whether the management of combat-related traumatic open fractures with early evidence of infection should include empirical prolonged therapy for gram-positive organisms, even if these organisms are not obtained by culture of the wound, to reduce the late occurrence of these organisms. Also worthy of additional consideration is the role of the prophylactic use of a first-generation cephalosporin at the time of surgical management of these fractures in inhibiting the growth of pathogenic gram-positive organisms from culture, potentially allowing the organisms to propagate within the wounds after the cephalosporin is discontinued, perhaps contributing to failure of union or other wound complications much later. It can also be argued that the development of staphylococcal infections is associated with exposure to these pathogens during the long rehabilitative phase of recovery or from the selection of *Staphylococcus* from the use of broad-spectrum antimicrobials to treat multidrug-resistant gram-negative bacteria. Although the scope of this study does not allow us to make any recommendations on these matters, they are certainly points that require further investigation, ideally in a prospective fashion.

The data from this case series of patients with type III tibial fractures show that early wound contamination is a frequent complication of fractures from war trauma. These early infections show a predominance of gram-negative organisms that are successfully treated and cleared. Recurrent infections tend to be due to staphylococcal organisms, and these infections are

typically associated with the morbidity of open fractures, including delayed union or limb amputation.

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